DR. MATSUMURA: I think it is a separate question of what should we recommend for abdominal films in clinical care of patients, and in response to the question of why there are few abdominal films, I think many clinicians will look at the data and say you have identified two fractures by films, 0.4 percent in the pivotal study; no clinical consequences. And, I think they may regard an abdominal film as perhaps something they will get as a baseline in case something happens, but not to be doing it with as frequent intervals or same intensity as we were doing in this research study where we want to capture anything that might happen in these rare events.

DR. PINA: You are not planning on including that?

DR. MATSUMURA: Do you want to address the labeling?

MR. WILLIAMS: We will share, as part of the physician training and labeling, what the clinical experience has been and the obvious benefits of rigorous follow-up. What is actually clinically applied and clinically practical, as Dr. Matsumura refers to, really does come down to physician judgment, but I think it would be the

responsible thing for the sponsor to share the advantages of the clinical research learning and that has provided us with a higher level of rigorous follow-up.

DR. PINA: I have no further questions.

DR. MATSUMURA: I know you want the break, but to go back to your impression on the Atlanta case, I do remember this very clearly because I had a phone conversation about this. The PI was called because the CT scan had this impression of lumen thrombus within the graft; ran down to look at the film; ran up to see the patient; and it was the PI's impression that none of the symptoms that the patient had were attributable to the intraluminal thrombus. There were pulses in the feet. The patient didn't have symptoms referable to limb occlusion. So, I think it was that clinician's impression that those symptoms were not referable to that lumenal thrombus.

DR. PINA: Well, they didn't actually sound like rejection but here is one where you should have a normal heart. I am using that as an example of somebody if you have a transplant, supposedly if they are not rejecting it their heart is still functionally normal, which is different

than your other population which has pretty sick hearts, it sounds like.

DR. LASKEY: Is that it? We are late in the fifth set and we have a lot of work to do here. There is some important discussion. So, I would suggest we make a ten-minute break please, and if we can all convene at 4:20 we can get onto the panel recommendations.

[Brief recess]

DR. LASKEY: Thank you for your promptness. At this point, we would like to hear the questions again so the panel can go through the process here. I am going to relieve our very responsive people at the table. If you all could, please step back from the table now; take a break. We would like to have the questions posed to the panel.

If I might, I would like to summarize where we are on each of the points put to us, and to try to summarize consensus and dissent. With respect to the first question, the primary safety endpoint was the rate of major complications by 12 months. The data are presented for individual adverse events. Analyses are provided for risk factors. Summary of the 24-month results is also

included. Please comment on whether the results of the clinical study provide reasonable assurance of safety in the intended population.

At the outset, I have to say that I don't know who the intended population is. It was never clear to me, as I believe Dr. Roberts was getting at and a number of other people were getting at. How many people are in the box at the very top of this schematic diagram? Before you get to the decision point as to whether they go into the control arm or the EBE arm, really how many patients were in the box before that that then led to this decision path?

Furthermore, it was always clear to me that everyone needed to be a surgical candidate, and that needs to be reflected in our thinking.

Members of the panel, is it fair to say that based on what we have heard today with respect to the safety endpoint the sponsor has met the goal of demonstrating safety? It certainly appears from the K-M curves, if that is the primary endpoint analysis, as well as the cumulative event rates that the adverse event rate was certainly significantly higher in the surgical control arm than in the EBE arm. So, do we have consensus on

that point? I think so. Good.

Number two, primary effectiveness--I can't strictly say efficacy because it is not a randomized trial, but primary effectiveness endpoint of the clinical study was exclusion of the infrarenal abdominal aortic aneurysm from the blood circulation, defined by absence of aneurysm enlargement and endoleaks, as evaluated through 12 months. Additionally, data regarding potential problems associated with endovascular treatment are presented. A summary of 24-month results is also included. Please comment on whether the results of the clinical study provide reasonable assurance of effectiveness in the intended population.

Again, I think we need to be very clear about the intended population, that every single one needed to be a surgical candidate. Secondly, I took away a significant amount of concern, if not dissent, that the primary effectiveness endpoint was not met to the level of statistical rigor defined prospectively, as discussed by Dr. White, Dr. Grey and others. That is from a statistical standpoint. From the clinical standpoint, is the 80 percent efficacy satisfactory to the panel? And, are we happy with the disparity in the unit of

analysis that went into the derivation of that number? I think not but can we have some discussion?

DR. COMEROTA: I will kick off the discussion at some risk. I think it is fair to say objectively there are not statistical results which would support efficacy. That has been decided on the basis of the sponsor's identification of what their endpoint was to be at the beginning of the trial, which was a rather high bar to set. If we look at were the efficacy endpoints reasonable and clinically meaningful, I think the answer would be yes. Dr. White pointed out discrepancies in ways of evaluating the numbers of patients at 12 months by the core lab versus the investigators. The absolute numbers are reduced by the core lab report. The percentage, however, reporting endoleaks does not change.

So, if we can assume that that is a reasonable look at the overall test group, then efficacy still does not reach statistical power. But from a clinically meaningful perspective, it probably does.

DR. BAILEY: Could I just bring up one question that I may have asked but I am now

confused again? Dr. White has educated me on how confused I should have been about the denominators, but I would like to inquire once more about the numerator for that efficacy. I am sorry that the company has had to step back, but if a patient had an endoleak at six months and it was treated, and they also came in at 12 months and it was seen to be negative with no endoleak at 12 months, are they in the numerator or not?

DR. COMEROTA: I don't think so. The answer to that would be no.

DR. BAILEY: In other words, efficacy then from that point of view is defined as no endoleak that cannot be treated within the first 12 months; that it is absent at 12 months?

DR. COMEROTA: An endoleak is absent at 12 months.

DR. BAILEY: Yes, but it may have to be treated in the interim.

DR. COMEROTA: If it was treated at six months and it is no longer present at 12 months, it is absent at 12 months.

DR. BAILEY: Right, and that is the definition of efficacy that we are dealing with.

DR. LASKEY: I suppose we can go back to

the panel pack and see how efficacy is defined. Was it a time to event or was it a cumulative event? In which case, I guess there is censoring involved.

DR. BAILEY: I am okay with that definition. It just needs to be up front that efficacy is not absence of ever having a leak; it is that you may have a leak but if you can treat it and it is gone at 12 months, then that is considered a success.

DR. COMEROTA: Or if it is identified, not treated and gone.

DR. BAILEY: Or if it is identified, not treated and gone, that is a success.

DR. LASKEY: Further discussions on efficacy? I am not sure we are going to, nor should we get around this issue of statistical versus clinical significance. I think people will vote with their feet on that one.

DR. WHITE: Let me just respond to Tony, and that is that not only did they not make the statistical efficacy but, more so, the lack of evaluation of 30 percent of the patients for at least one of the endpoints, the endoleak business, means that there is an underestimation even of the

numerator and we know the minimum number of patients.

We also know, as I believe Dr. Freischlag pointed out or maybe it was Dr. Najarian, that in the second year there are actually more of these appearing and worsening of the size of the aneurysm, more enlargements. It seems to be progressive over the second year. So, when we ask ourselves is it clinically important that they meet the 80 percent arbitrary number, I find the fact that they failed in that regard to be very significant and I would not, as Tony is suggesting, dismiss the importance of the statistical efficacy. I think we are missing a big chunk of these patients and we could be surprised with some really bad numbers if we knew the whole numbers.

DR. LASKEY: In fact, the point estimate might be well below 80 percent.

DR. WHITE: Right.

DR. LASKEY: Third question--

DR. ZUCKERMAN: Dr. Laskey, this point about what the panel believes about clinical versus statistical efficacy is an important one for any approval decision, etc. So, is it possible to hear from other panel members on this point?

DR. PERLER: Well, I have a question. Is historical precedent of relevance here in terms of other devices and where the threshold was set in terms of clinical and statistical efficacy? If that is an inappropriate question, I withdraw it. If it isn't inappropriate, what was that threshold?

DR. ZUCKERMAN: Each PMA should stand on its own. I think why we are at a panel meeting here is that it is obvious that the primary endpoint was not met from a statistical basis, but there is a wide amount of historical literature now available. So, you are asked as panel experts to comment on the observed results with their confidence intervals and make a guesstimate as to what you think of it.

DR. LASKEY: Warren, can I ask you a question?

DR. LASKEY: Yes?

DR. AZIZ: This is the 40 patients in whom the CT scan could not be interpreted for endoleaks. It may have bee at six months or a year. I don't mean to sort of cloud the argument, but could those 40 patients--could we ask them to, in the near future, repeat the CT scans or would that muddy the water? I mean, it is not like it can't be done.

DR. LASKEY: Well, it is certainly off protocol to do it at this point. I guess, from my standpoint where the rubber meets the road here, the decision that we have to make is based on the adequacy of the primary data. If we do not have an adequate number of evaluable patients, and 80 percent is usually the magic number in our business for restenosis studies for example, if you don't have an evaluable number of patients, then the point estimate you come up with is highly uncertain. And, I think that is what we are struggling with here. The core lab study number is not adequate for our standards to make a meaningful decision. That I think is at the heart of it. So, doing the studies at this point I don't think would be terribly helpful. Is the agency satisfied with that deliberation of statistical versus clinical? We need an adequate database to make an informed decision.

DR. ZUCKERMAN: Right. What I would like to know, from the agency's viewpoint, is whether that is the consensus opinion of the panel for answering this question, or is there a significant amount of division.

DR. FREISCHLAG: I guess what I am

wrestling with is I wouldn't have a problem if they were close if we had all the data. I guess that is everybody else's point. If we had every single piece of data and they missed it by a little, then I guess I would go into the biological versus the statistical and feel pretty comfortable that I was all right with it. I must admit, I thought I wasn't confused until we kept talking, and I think there is a confusion about how many scans and all that, and that is what has gotten me befuddled as we kept counting. If we added all of them and it was close I would feel much more comfortable sort of saying you are close. I am real uncomfortable with missing data.

DR. LASKEY: I think it is fair to say we all are. DR. ZUCKERMAN: Okay.

DR. LASKEY: And, that that precludes a definitive decision on the clinicians' part.

DR. ROBERTS: I guess I would say that I would sort of echo what Dr. Freischlag just said, which is I would be much less concerned I guess if I knew that they just--you know, obviously you set these numbers up ahead of time. You are going sort of a priori; you are not really sure probably exactly what you ought to be aiming at. So, I

wouldn't really be too concerned statistically about this. I think clinically, my concern just rests in terms of do we really know what happens with these patients, and if we are missing some of the data points then, you know, we have to be concerned about is this really something that is going to be effective.

On the other hand, to some degree, you know, there are devices out there, both for this application and other types of applications, where part of the clinical use of these isn't 100 percent. You don't, for sure, know what all the data is. I think this is where I get really concerned in terms of the labeling and in terms of the education of both the clinicians and the patients to understand that, you know, the science only gets us so far and we really don't have the long-term data. Even if we had all the data points for this two-year study, we still don't really know what is going to happen in year three and year four and year five. So, to some degree, I think we have to understand that we are dealing with some uncertainty here even with all the data.

DR. LASKEY: That is true, Anne, but those are very different issues than deciding on a

12-month endpoint which doesn't have an adequate number of patients at that endpoint.

DR. ROBERTS: That is still the reality.

DR. LASKEY: Yes. Again, Dr. Zuckerman, I am not sure we are going to demonstrate consensus at this point in time. That may be reflected in the way people vote but it is obviously a fundamental issue. Can we move on?

DR. ZUCKERMAN: Yes.

DR. LASKEY: The third question, please. Core laboratory has reported two cases of wire fractures, one identified at discharge from the pivotal clinical study and the other at 12 months in a patient enrolled in the second generation device study. There were no adverse events associated with either report, but there is no conclusive evidence to verify the presence or absence of the fractures. Both reported fractures were identified in the main body of the graft, not in a seal zone or point of attachment to the aorta.

DR. PINA: Warren, I would like to ask some of my vascular surgeon colleagues how comfortable they are with this because I know that is something that would trouble me.

DR. LASKEY: Let me finish. You are

right, this will come right out of this continuation. After the packs were sent to the panel, the sponsor reported an additional wire fracture which was recently identified during analysis of a device explanted in Germany. Details concerning the length of the implantation, etc., etc. remain unavailable. Based on the sponsor's analysis it appears that the fracture, which was also located in the main body of the graft in the crotch of the bifurcation, did not result in any clinical complications. Please comment on the significance of these observations.

DR. PINA: Again, I would like to ask my vascular colleagues, maybe Tony or Dr. Aziz, what they feel about the fracture issue since I am not a surgeon.

DR. COMEROTA: Warren, you are looking at me.

DR. LASKEY: No, actually I was watching the interchange. The question was put to Dr. Aziz and --

DR. COMEROTA: He patted me on the back.

DR. LASKEY: Yes.

DR. AZIZ: I do mainly cardiac surgery. I am not really an expert to make a real comment on

that. But it would really depend on what effect does a fracture have on, let's say, what the device is trying to achieve, it seems to me. I mean, if you had a fracture and it didn't have an effect on the aneurysm enlarging or rupturing or endoleaks, then I think it may be sort of a true unrelated phenomenon. But if it fractured and it meant that the device was malfunctioning, then I think to me it would seem that that would be an important factor.

DR. COMEROTA: The answer to the question is that I don't know that we know what the significance is, other than that it was not clinically significant up to the point that it was identified. I presume those patients will continue to be followed since it was an incidental observation as part of the follow-up phenomenon.

DR. PINA: What concerns me is that it sounds like the core lab identified it and the investigators did not. That goes back to my question, what is the best way for the clinician, once they insert these, to look for things like fracture. I mean, I am comfortable with the fact that they were in the body and not in the junction points.

DR. COMEROTA: Of course, there are some endografts that have no external support in the body of the graft; it is only at attachment points. So, again, the relevance of that observation I think we don't know yet.

DR. NAJARIAN: I think you would have to look at the clinical sequelae. I mean, if every single one that was implanted had a fracture in it but, yet, there were no clinical problems I would still have no problem with it because devices we put in all the time and sometimes they do break; catheters crack but there really is no clinical problem with that. It sounds awful. I believe the metal is just used to support the graft and, just looking at it, I can't imagine that one fracture would actually affect the integrity that much and, if it did, we would know or we would know in time.

DR. AZIZ: Wasn't there a stented graft that had fractures and was withdrawn from the market?

DR. ZUCKERMAN: You know, as previously mentioned, I think in an ideal world one would like to design a device such that there are no fractures and no concerns about clinical sequelae. As to whether in this case there is a different threshold

is the question before the panel. Could we consider an approval based on a device that doesn't have 100 percent device integrity without clinical sequelae? Yes, but we need to hear from the vascular surgical experts and interventional radiologists as to why that is okay. You know, Dr. Najarian gave some comments and so forth.

DR. PERLER: I think we could, but I think we must expect that there will be much more consistent KUB follow-up of this cohort through five years. I think the other issue, at the risk of opening a Pandora's box, is that probably CT is not as sensitive as plain old KUB for looking at this potential complication. That was another area where there was less data than with CTs, and certainly that would be something that would have to be done, if this is approved, for the five years to follow.

DR. ROBERTS: The only question I would ask, and maybe it is not known, but why was this one explanted? I mean, why did it come out? I mean, it is one thing to see it on a film and we know that that didn't seem to have, you know, any consequence in terms of how the patient did but I was just wondering if anybody knows why that one

was explanted.

DR. LASKEY: I think we would have to ask the sponsor why that happened.

DR. ROBERTS: Can they respond?

DR. LASKEY: Maybe the short way to do this is to have the sponsor respond in two sentences. Could you do that?

MR. WILLIAMS: Can they be long sentences?

DR. LASKEY: Yes, not run-on though.

MR. WILLIAMS: This particular device was explanted because the patient had a contained rupture and the patient had a surgical conversion. That is one sentence. My second sentence is that the sponsor would like to request some additional time to discuss the statistical issues, please.

DR. LASKEY: Okay, we will do that at the end of all of our questions. I know that doesn't answer the question.

DR. ROBERTS: No, it does answer it. I think the other two fractures, and obviously we don't know enough about this but the one thing I would say is the other two fractures apparently had no clinical sequelae. This, I am assuming, is a fracture that presumably did have clinical sequelae in that the patient had a contained rupture. So,

that is concerning.

We know this is going to happen. I certainly echo what everybody else says, that certainly we know that these things break in the body and it just goes back to the importance of follow-up not only for the study cohort but for the rest of it. I think it is very important to remember, and again what Dr. Perler said is true, that you can't follow these on CT. It is very hard to follow fracture of the metal within these because you are cutting across the same spot as the metal is and you maybe get it; maybe you don't. So, they really do need careful follow-up with KUBs to know whether it is fracturing. I think that will be certainly an important part to put in the labeling and the patient education and in the educational materials for clinicians who are going to be putting these in.

DR. WHITE: Could you comment on the ability to reconstruct the 3D CT? I have seen some beautiful reconstructions of aortas and it seems like that might be an excellent way to look at the footprint of the graft. Would that do it better than a KB?

DR. ROBERTS: It depends on how carefully

you do the reconstruction and whether you completely reconstruct the whole area; whether or not you have a lot of calcium in the way. You know, you may be able to do it but you may still miss it.

DR. LASKEY: To answer your question, there may be some clinical significance to these observations. We don't know. The event rate is small enough and the denominator large enough to make it difficult to make cause and effect, one to one, but we are concerned.

DR. ZUCKERMAN: And, Dr. Roberts, you may want to look at page 5-129 quickly regarding the German case.

DR. LASKEY: But to put this into, hopefully, some final perspective, these are three fractures identified over--what would be the denominator then? Not that we shouldn't be concerned about three fractures. What did you say the number of implants was that you might have a handle on? I know that they weren't routinely KB'd and routinely CT'd. If this were standard postmarketing surveillance, what is the number?

DR. MATSUMURA: There was one in the 235 patients. Of the three worldwide, there were 4400

patients with over 10,000 implants.

DR. COMEROTA: What is the number of KUBs? That is the denominator.

DR. LASKEY: Right, the number that were KUB'd.

DR. MATSUMURA: The number of patients with KUB in the pivotal study at a given time point is in the panel pack, 70 percent. There were 229 out of the 235 patients who had a KUB at any time point in the core lab.

DR. LASKEY: Thank you. For the fourth question then on the labeling, one aspect of the premarket evaluation of a new product is the review of its labeling. Labeling must indicate which patients are appropriate for treatment, identify potential adverse events with the use of the device, and explain how the product should be used to maximize clinical benefit and minimize adverse events.

Again, at the outset I think it should be stated clearly, and I don't think it is, that all the patients in the pivotal study needed to be surgical candidates, and that all the information derives therefrom.

In terms of whether there was panel

consensus on which patients are appropriate for treatment, we have had the anatomic criteria delineated. I am not sure we have had the clinical criteria delineated. And, I think we should have some additional discussion about potential adverse events with the device, including fracture, wire fracture, and how the product should be used to maximize clinical benefit. I certainly don't think at this point there is consensus on this issue. So, let's start with which patients is this appropriate for. Do we feel that there is enough information in the IFU right now, as is, to make that perfectly clear? Dr. Roberts?

DR. ROBERTS: Well, I think there is a fair amount of data. I think the issues that I would have would be standard ones in terms of having an aneurysm, obviously having a neck that is within the standards of the 1.5 cm, having suitable landing sites for the distal portion of the graft. The one thing that I think I would like to see strengthened is that I am a little bit concerned about the size of the iliac vessels.

DR. LASKEY: So, adding dimensional data with some reasonable degree of precision?

DR. ROBERTS: Yes, I think that would

probably be a good idea, or at least rather than just very vaguely spell out iliac morphology, instead to perhaps either, you know, give some kind of a size indication and also something about the morphology in terms of the calcification and the tortuosity of the vessels.

DR. LASKEY: I know we have heard from Dr. Aziz and others that likely to be the case is that this device will be pushed, the technique will be pushed, and that it is likely it will be tried in patients that are not included in this kind of trial. Does anyone share my concerns about insisting that the language read that the patients need to be surgical candidates? That is certainly the way the protocol reads. Do we want to carry that through the IFU?

DR. PERLER: Well, I think there are very high risk patients for open surgery for whom endoluminal grafting is a real benefit. I would have a problem with that wording.

DR. WHITE: I think though the reason that it is brought up--I wouldn't argue with you but I think we don't know the performance of the device in that population. My problem is whether or not I think there is efficacy data to say that this

device is equivalent to open surgery. I mean, basically we are being asked to say that the device qualifies as an alternative to an open surgical procedure in a patient who is a surgical candidate and I think there is a question about that.

DR. COMEROTA: I think the issue is a little bit different there, Chris. These are good risk patients that were evaluated in this trial so that they can be longitudinally followed over reasonably long periods of time.

DR. WHITE: Tony, they weren't good risks though because they were ASA all the way to Class IV.

DR. COMEROTA: Correct, but sharing Bruce's concern about modified wording, the patient that we would most like to have this available for, or any alternative to an operation available, is the patient that is not likely to live for two, three and four years but is at very high risk of rupturing their aneurysm in the immediate future and if you have an effective device that can be delivered safely, then that would be a good alternative to not operating.

DR. WHITE: But nothing that we are going to do today would stop you from using an approved

device in that individual patient.

DR. LASKEY: There is no question what you say is true, Tony, but we have no data before us to support that. That would be a different study. Ileana?

DR. PINA: I am not sure that in the IFU packet there is a descriptor of the control group from the pivotal trial of who are more likely to be symptomatic, which is why they were taken into the surgical arm instead of getting the prosthesis, and I think that that needs to be stated there, that this population was largely not "symptomatic" if there is such a thing as symptoms. I agree with you on that, Dr. Freischlag.

DR. FREISCHLAG: I also think for use of this graft that you don't need to be a surgical candidate. I guess my concern is size. You know, it doesn't really even say you have to have an aneurysm in their labeling. You assume you are going to; that is why you are using it. But whether or not size needs to be suggested in the labeling too--I guess you could argue, you know, that a 3 cm aneurysm is an aneurysm but I think we have data with that, and I don't know the answer to that but I think I would be more concerned about

the size rather than the surgical candidate piece because that is what the physician is going to decide.

DR. ROBERTS: I, quite frankly, would disagree with this idea of saying that they have to be a surgical candidate. I honestly think that boxes people in and I don't think that is really a reasonable thing. I think it is what was done for the study, and I think it was an appropriate thing to do for the study because it allows for a control group but I don't think it ought to go on the labeling.

On top of that, quite frankly, I am much more worried about the patients who are surgical candidates and whether or not this is the right thing for them. You know, if you have a young 50-year old who has an aneurysm, is this the right thing? And, that we don't have the answer to. But I don't think we ought to limit it to people who are surgical candidates.

DR. ZUCKERMAN: I think it is necessary to understand that when we are writing an indication statement for this PMA device, it is important that the indications statement reflects the clinical trial data because that is where we know the data

are. Now, several people have spoken about how this device might perhaps work superbly in other patient populations, but that is not the point under discussion today for the indications statement. We have a PMA clinical trial and we need to use those patients and data to write an indications statement.

DR. LASKEY: While I appreciate the discussion, I think the mission here is to adhere to the spirit of the protocol, and we cannot go beyond the lessons learned from this protocol, much as we would like to use these in patients who are critically ill and not surgical candidates.

DR. ROBERTS: But if I am reading what you say correctly, Bram, what you are saying is that the indication for use for the Excluder Endoprosthesis is intended to exclude the aneurysm from the blood circulation in patients diagnosed with infrarenal AAA disease who have appropriate anatomy. It says absolutely nothing about whether or not they are surgical candidates or not. If we are asked to comment on that, I would agree that that at least begins to define it although I would add that probably it wouldn't be a bad idea to put something in terms of how big the AAA is, and also

define the appropriate anatomy a little bit more to make sure that people understand that they have to worry about iliac arteries and that kind of thing.

DR. ZUCKERMAN: Yes, let me make some suggestions as to what we do in situations like this for other stents, such as our coronary stents. One is that we can make a better effort, as I have heard, to define the dimensional measurements of the vessels so that we know the patient population. Mr. Gantt is also going to show examples with other approved devices as to how we better specified the intended patient population. Sometimes we just describe in the clinical trial section a better description of what was studied and put in parenthesis in the indications statement "see clinical trial section." But, you know, we are here to try to better describe and indicate this device for what it was studied for today.

MR. GANTT: If I may, I can show you the other currently approved indications for use statements.

DR. LASKEY: I certainly think it is instructive but I don't think it should bear on our decision based on the data in front of us, but it is certainly very instructive. Thank you.

[Slide]

MR. GANTT: Another example refers to anatomic considerations, not clinical indications. Okay?

[Slide]

One final example.

DR. LASKEY: So there is some attempt to quantitate, or at least to provide dimensional data. That is helpful. That is very helpful. So, I should not be concerned about the fact that we are not going to use the language that they need to be surgical candidates even though that is the way this protocol was written.

DR. ZUCKERMAN: You can make that suggestion.

DR. LASKEY: Thank you. Have we achieved consensus on using the device to minimize adverse events? I think so.

Question 4(a), does the indication for use, as stated below, adequately define the patient population studied, and for which the device will be marketed?

The Excluder Endoprosthesis is intended to exclude the aneurysm from the blood circulation in patients diagnosed with infrarenal AAA disease who

have appropriate anatomy. I think here we can build on lessons learned and add some of the quantitative dimensional data. Agree?

Question 4(b), based on the clinical investigation experience, are there any additional warnings, precautions, or contraindications that you think should be included, either specific to this device or from a generic standpoint for endovascular grafts?

I will just lead off. Since we are on the theme of looking for fractures, I don't think we know the estimate of their frequency with any precision and I don't think we know their clinical significance. So, we need to continue to acquire data along those lines.

DR. PINA: Warren, I think that we should also add that endoleaks can happen early. This may be true in other grafts, as I have heard, and these may need to be repaired early; and some can appear even later, beyond the 12 months.

DR. LASKEY: Right, that this device confers the risk of endoleak and, therefore, additional intervention. Good.

DR. PERLER: I think there should be a statement that the safety of bilateral internal

iliac artery occlusion in the deployment of this device has not been established.

DR. LASKEY: Anything else?

DR. COMEROTA: Are you talking about this device specifically or the general concept of bilateral internal iliac artery occlusion, Bruce?

DR. PERLER: Both.

DR. LASKEY: The question is open-ended.

DR. PERLER: But in this study that was an exclusion criterion. Apparently none of the patients had bilateral hypergastric exclusions so I think that ought to be stated in the labeling.

DR. ROBERTS: I would go a little further than just the KUB and I would just say that KUB and CT scans need to be done on at least an annual basis, and I would like to actually see something in the labeling that says that we don't have long-term follow-up on these devices and careful follow-up of the patients is mandatory.

DR. COMEROTA: What about using an alternative imaging technique, other than CT, such as MRI may be substituted?

DR. ROBERTS: Yes, I was looking at this as more generic but I think actually this device may be one that is well suited for MRI evaluation

because of the fact that it is nitinol and I think you can actually see--some of the ones that have stainless steel you are not going to be able to do that but in this particular device I think MR may be a very good way to follow them. But, basically they need to have some cross-sectional imaging follow-up looking for endoleaks which can develop late, or aneurysm size change which can occur late. Quite frankly, I am concerned about the fact, and it is not unique to this device, that the aneurysms continue to grow even at two years. We don't know what they are doing at three years, and they can continue to develop new endoleaks in some of these patients.

DR. LASKEY: Therefore, this kind of radiologic follow-up is strongly recommended. I am not sure we can say mandated, though we feel that way.

DR. FREISCHLAG: I think also that needs to be done for migration issues because in some of the other grafts they have noted migration late out. So, you can add that word into it. It may be helpful for people to know that, even though there wasn't much seen here.

DR. LASKEY: I guess we ought to add late

migration then to some of the risks. I am not sure we mentioned that specifically in one of the prior questions.

Question 4(c), please comment on whether the instructions for use adequately describe how the device is to be delivered.

I don't think there was much dissent on that. It is pretty straightforward, complicated but straightforward.

Question 4(d)--do we have other comments?

DR. PINA: Warren, let me ask a question about labeling. In the labeling where you have a descriptor, like, in a drug side effect profile, can you add the cause of death? Deaths have been reported, you know, so many with this; so many with that. Can you do that?

DR. ZUCKERMAN: Yes, typically in our adverse events section we will summarize the deaths, number and percentage and, to the best of our abilities, what the causes of death are thought to be.

DR. LASKEY: Number five is asking us to comment on the adequacy of the proposed physician training plan.

DR. WHITE: I have a question for the

surgeons, and Tony maybe specifically, they don't discriminate in the training plan between and operator who is already practicing these devices and a newby. Do you think that it would be appropriate to discriminate between somebody who is already credentialed to be doing this in their hospital and what it would take to do this safely, and what it would take for a newby who wanted to get into this business?

DR. COMEROTA: If I am not mistaken, Chris, in the plan their initial approach is to, obviously, integrate those who are already doing the procedure and who already have participated in the trial, and then move out to others.

DR. WHITE: Right, I guess the question is if they move to somebody who has never seen the device before but they are already implanting exclusion devices, should the training for that person, stranger to this device, be different? Should you discriminate from the person who just comes in and says, you know, I would like to put in stent grafts for the first time?

DR. COMEROTA: Well, I think the obvious answer from my perspective is yes. I think there ought to be a difference because you are looking at

an endovascular education versus a device education, and there are polar differences there.

DR. PERLER: But my understanding of the program is that there is going to be an assessment of the prospective user in terms of their ability to select patients for the procedure and their performance of the procedure under proctor's observation. Presumably, that is going to determine who gets access to the device.

DR. COMEROTA: But the proctor is often the seller. One of the other things that is going to supersede all of this is that the credentialing at the institutional level. So, no matter who the manufacturer of any device is, if the physician who is going to implant it doesn't have appropriate numbers for implantation, they can get all the education they want but they are not going to use it.

DR. WHITE: So, are you saying that the labeling should say that initially the purchaser must be credentialed to do this?

DR. COMEROTA: No, I don't think we can get into that at all. That is at the institutional level.

DR. WHITE: Well, no, I am not suggesting

we design the credentialing criteria; I am saying that if you are going to sell this device to a doctor, should the doctor already be credentialed at that institution in order to be a customer? Or, should we stratify the training for the physician who is not credentialed but who wants to learn how to put in this device? Should he go through a different training program than a guy who is already up and running? That is all. I think that is simple, but I don't think it has been addressed here.

DR. LASKEY: I think a better term is experienced rather than credentialed since that is the governance of the local institution. Anne?

DR. ROBERTS: I am sorry, but if I could just go back to the labeling again, the one thing that was not clear to me in the labeling is how much overlap there should be when you put in the contralateral prosthesis when you go up the other side. It is not clearly outlined in here as to how much overlap there should be. They talk about the extenders and they talk about how much overlap there should be, but it is one thing that ought to go in the labeling. You know, what is the ideal amount of overlap, at least the minimum amount of

overlap to avoid having these components come apart.

DR. LASKEY: That is back on 4(c), okay, great.

DR. ZUCKERMAN: Dr. Laskey, there have been lots of comments on what can be said about the proposed training program and the label. Usually we indicate that physicians should have undergone a training program and leave it at that.

DR. LASKEY: I notice the language in the panel pack discusses institutional volume. I am sure that would not necessarily be reflected in writing but that will be a priority of the sponsor? I mean, the center needs to do an adequate number of cases to demonstrate proficiency. So, I think that may take care of itself but it is difficult to write into language institutional volume. But these generally will be high volume centers, or should be.

DR. WHITE: Why do you say that, Warren? There is no reason to believe that these will generally be high volume centers. Every vascular surgeon in this country is aware of the need to offer the alternatives so I don't see any reason for that.

DR. LASKEY: They may not have access to the device, depending on the criteria put down by Gore et al. One can only hope that that attains in real life.

Number six, the sponsor proposes a post-approval study on the patients enrolled in the pivotal clinical study. Five-year follow-up on all patients who are alive and not withdrawn from the study will be obtained in accordance with the clinical protocol approved. Please comment on the acceptability of this plan.

I think every member of this panel is in agreement with that and calls for extended follow-up. I don't know why you want to exclude patients withdrawn from the study. You may just want to include everybody.

DR. BAILEY: At least for vital status. I don't see why you can't get vital status on 100 percent.

DR. LASKEY: Correct.

DR. PINA: Well, there are issues out there right now about if patients have withdrawn consent if you can even go check up on vital status. That is going on in several institutions right now.

DR. LASKEY: If you are alive and provided consent to participate?

DR. PINA: Yes, usually that is very true. At our IRB out in Los Angeles, if somebody withdraws from the study you are not allowed to say hello to them in the hallway. So, once they withdraw, that means they don't want any further contact. So, right now that would be a very big problem in a lot of centers, even though it is in their best interest to be followed.

DR. LASKEY: Well, with that proviso, I think we are all in agreement that there should be five-year follow-up that is as inclusive as possible. I believe that is it for the panel questions. Am I correct?

At this point, I would like to give some additional minutes to the sponsor and then, if needed, to the FDA. If you have additional comments or questions before the vote, please step forward.

DR. ROBERTS: I am sorry, I guess I am still on West Coast time so there is a delay here. But I am just wondering about the patients that the sponsor has, in fact, enrolled in this study that were sort of additional patients that they got

permission to continue putting this device in, I am assuming that all the data has been collected on those patients as well. So, it would seem to me that those patients who have, in fact, been enrolled even though they are not counted in this group probably ought to be also followed because they are just more additional patients.

DR. LASKEY: That may be true from a scientific standpoint but, Dr. Zuckerman, can you clarify some of the regulatory aspects of this?

DR. ZUCKERMAN: Well, if the continued access registry is basically following the same protocol and the panel believes that there is a scientific reason, underlying scientific reason to obtain more data and that is an obtainable data set, then that is one possibility if the panel suggests that this device should be approved with postmarket surveillance. But I think the key thing is that one wants to define, first of all, the question of whether one needs additional data, other than the numbers talked about on the slide which come from the original PMA cohort. You know, there are costs and other factors involved with looking at additional data sets.

DR. ROBERTS: Well, I guess I wouldn't be

completely strong on it but it seems to me that these were patients that the FDA allowed Gore to continue to place the device in despite the fact that they had already finished their enrollment. They are patients that, in fact, are being enrolled in an experimental protocol. They are patients that we can get data on, and given the fact that we know that there is going to be lots of data from patients as they go along the trial, and we have already seen that and we have already said, well, gee, you know, we were not completely comfortable with some of the numbers, it seems to me like this might be one way to kind of get around that uncomfortableness with some of the numbers.

DR. ZUCKERMAN: Right, and that is fine if you can define the reasons why you want additional data.

DR. LASKEY: I made an egregious procedural error, gentlemen. Please forgive me. I need to get comments from our representatives from industry and the consumers at large. I invite you back to the table. Please forgive me.

MR. DACEY: I was very interested in hearing the comments on the patient labeling document and physicians because they echoed some of

my own concerns. I would like to make it clear that I have spent many professional years preparing patient education materials, and I have changed my thinking over time.

The materials that I have seen more and more, including some of this, are that one side fits all category. Even though where we are getting the same demographically, socially and culturally, the patient population is being much more, both broadly and specifically, defined and everybody is trying to communicate to them. When I see a document such as this patient document going to the web site, I am beginning to see more and more marketing and less information.

I saw the brochure. It is very well documented but what I am seeing is a cure, not a treatment as soon as you start seeing the smiling faces. It is not unlike what we see on the six o'clock news with pharmaceuticals. You know, everybody is offering a cure but not defining the treatment. And, there is a whole bunch of responsibilities downstream.

So, I have been studying more what is happening in the social sciences, the neurosciences, and I would encourage the FDA and

sponsors in general to start looking at what works and what doesn't work, and really helps a clinician and what really promotes the partnership, and define some responsibility at the consumer end. Consumers really need to know. When consumers become patients they put a great deal of faith in the science and the practitioners of the science have to make sure that the patients understand.

I understand all the informed consent issues and all the new HCFA issues, but the basic thing is we have to raise awareness; we have to inform. But when you get into education it becomes a whole new domain that is interactive, and what they are finding in a lot of cases, especially if you have to ask people to change behavior, is that the only thing that works is tutoring. You can't tutor every patient that comes through a clinician's door.

So, I think we have a whole new opportunity unfolding, and who knows, in our post-modern world that is shaping up, patient education may eventually becomes sort of virtual reality. But I would like to effuse, if I could, some of the marketing thrusts that I am seeing in these kinds of materials where everything is a cure

and not a treatment. That is all I have to say.

DR. LASKEY: Thank you, Mr. Dacey. Mr. Balo?

MR. BALO: From an industry perspective, I would just like to say I think the FDA, the industry and even the panel today really had a very vibrant discussion about all the facts and about the data.

One of the things I think the panel should consider here is that when industry goes into a clinical trial--if you look at some of the data that Gore has presented today, it does show that from a safety perspective it is equivalent to what is currently being used for open surgery and for other graft procedures.

In addition to that, we keep on talking about, from an industry perspective, just like Mr. Dacey just said, what is good for our patient population. If you look at some of the other subset data relative to time in ICU, time to ambulation, time basically that you are spending on a patient, taking care of him after a procedure, obviously the graft procedure, the less invasive procedure, basically improves upon that.

And, one of the things that a device

company tries to take into consideration is improving care for the patient, not improving procedures for the physician. I would encourage the panel to think about that and also take into consideration some of the other data that the sponsor has presented today which would be beneficial to the patients.

I would just like to thank everybody for the opportunity to be in this discussion and to learn a lot about statistics that I really didn't know before.

[Laughter]

Open Public Hearing

DR. LASKEY: Thank you. Is there anyone in the audience who wishes to address the panel on today's topic in this portion of the open public hearing? Yes, sir, please step forward and identify yourself.

DR. OHKI: My name is Dr. Takao Ohki. I am one of the local PIs, site PI, and I have hands-on experience with the Gore Excluder graft and, from that standpoint, I wanted to make a brief comment. I also have experience with maybe five or six other endografts.

There were only 19 sites I think in the

U.S. which were involved in the EBE trial, and we were fortunate to be one of them. Because the Gore graft had such a unique advantage over the other five or six devices, there were many patients that traveled to our site from other states. I wish that the panel does not dismiss this valuable device from becoming accessible to the American population just based on some statistics. I have seen patients' lives being saved because of this device. Thank you.

DR. LASKEY: Thank you, sir. One more? Name, affiliation and potential or real conflict of interest, please.

DR. FELLINGER: My name is Mark Fellinger. I am a vascular surgeon, from Dartmouth. I am a local site investigator as well. I otherwise have no conflict of interest.

I want to reflect a little bit of Dr. Ohki's comments. As a site investigator for many different devices, I have had experience using this device as well as both of the commercially approved devices and other devices currently in clinical trials. I think that overall some of the discussion about statistics and that sort of thing, I mean, I think it is very important to get the

statistics right. I think it is also very important to look at the adverse event rate. It is dramatically different. The acute recovery, some of those things, were dramatically different. And those things shouldn't get lost in discussion about specific statistical issues. I think it is also important to get the statistics right.

But one thing I can kind of reflect about, kind of dealing with this company and this group of people, my experience with them has been very good in terms of I think they have tried very hard to get the statistics right, and I don't think there is any effort here to misconstrue the data in any way. I think that is important, at least from my perspective. I think that is incredibly important whenever I deal with a manufacturer, and I won't deal with one that I think sugar coats the data. I don't think they have done that and I thought it was important for somebody that has kind of been involved in the process to kind of say that. Thanks.

DR. LASKEY: Thank you.

DR. GREENBERG: My name is Roy Greenberg and I am the director of the core laboratory at the Cleveland Clinic, and also a vascular surgeon that

has a large experience with endovascular implants.

I just wanted to address a couple of issues, one of which relates to the fact that I don't think that anything that was presented in today's data, or anything that I have seen with respect to the Gore Excluder device is different with respect to the fracture rate, endoleak rate, migration rate or any other radiographic piece of information that we can say is present in the two commercially available devices.

I also think that the interpretation of fractures with mechanical devices is something that we have to be very careful about because it is my contention that all mechanical devices will eventually fracture if the patient lives long enough when we implant them, whether that is a heart valve or a vascular graft. And, a fracture rate of three percent or two percent or one percent is a very low rate associated with any clinical significance. To ask to see a large number of fractures to show if there is any relevance clinically is going to be a very difficult thing for any company to provide.

So, I look at this, if I can extrapolate just a little bit in terms of the statistical

issue, not being a statistician, but the real problem here was in the original study design with respect to coming up with a number, which was 80 percent. I would hate to see a device that compares equal, in my opinion, to other devices that are already on the market or that are under investigation to not be granted approval based on a study design that was done five years ago. Thanks.

DR. LASKEY: Thank you. Are there any other thoughts? Is Dr. White coming forward?

DR. RODNEY WHITE: Thank you. Again, my name is Rod White. I am a vascular surgeon, from Los Angeles. My conflicts remain the same, and again, my greatest conflict is I make my living doing this and I think that is the most important thing for everybody to keep in consideration.

The topics you have brought up are obviously of great interest, but I think there are two issues that need to be looked at. One is that in any of the other studies that have been done like this, and there is an ongoing problem that the data set that the core lab has is reliant on several things: It is what they get from the centers. Usually the quality of that data is not as good. Actually, the percentage that have been

evaluated or can be evaluated in many of these, if it is 70 or 80 percent it is pretty good. So, I am not troubled by that number in particular.

I think what needs to be looked at and the greater consideration is that the data sets that lead to the clinical treatment, what physicians treat these patients related to, are the x-rays. If there is a leak or some abnormality, that clinical data set is generated on the clinical set, not the core lab set. That comes later and does not have an impact on what is the efficacy data that has been presented.

So, my take, and I don't know because I am not an investigator in this study and have only an overview of the other data sets globally, is that probably 95 percent or better of these patients did have studies and that the clinical treatment was based on what the physician saw that day when they saw it, and that algorithm is what the data set is relevant to.

So, I understand Chris' point about the core lab set and its relevance and what percentage is there but, again, that number means that 70 percent of the data was interpretable and that should match what the other data sets are provided

by the manufacturer, and from what I have heard today I think they do that.

But I would remind everybody that when you are in an acute situation you get the studies, you intervene and the data set you are evaluating is based on that clinical data set and the core lab comes in later and verifies that but has no relevance or impact on the clinical data set itself. I think that is one of the issues that has to be looked at in any of these studies. The core lab is an important data set but it doesn't determine the clinical treatment.

The other thing that has been a relevant consideration is whether or not this represents what is the state-of-the-art and the patient need. I must say to you again, just from a conflicted person who takes care of these patients, the patients have looked at this information and in their own mind feel that this is a very important therapy and that is one of the reasons that it is clinically available. So, I think it is an important study and the manufacturer has done an excellent job of presenting it. Thank you.

DR. LASKEY: Thank you. I think we can all agree that a clinical trial design should be

both scientifically valid as well as trying to mimic as much of the clinical reality as possible. Thank you. Any other comments? If not, then I would like to close the open public hearing and ask for any final comments from the FDA.

Final Comments from the FDA

MS. ABEL: I am Dorothy Abel. I am one of the lead reviewers on this document and actually have been involved in the review of these devices since their inception, probably longer than anyone else in the room.

One thing that I think is clear is that over time the more we learn about these devices, the more we learn that we focused on the wrong thing over time. What we have attempted to do is to find some useful surrogate endpoints to evaluate whether or not these devices are effective in avoiding aneurysm rupture.

Now, we can't design studies to look at aneurysm rupture. Many years ago when we started to look at these studies we thought we would look at aneurysm exclusion because, obviously, if it is not excluded there is still the potential for rupture. What we have learned over time is that endoleak in itself doesn't appear to be a good

surrogate endpoint and I think that needs to be taken into consideration when you are concerned about how complete that particular piece of information is.

I think we are still struggling with the best way to evaluate these devices, but I just want to caution that, again, this was a definition that was made sometime ago and you need to think about the state-of-the-art with respect to the definition of success with these devices. We actually have some companies that have retrospectively gone back and said in our PMA we are not only going to evaluate the data in accordance with the way that we designed the study many years ago, but we are also going to do these additional analyses because they are more appropriate according to what we know now.

This company didn't happen to do that. I think possibly it would have been a good idea, and maybe we should have asked them to do that because then you would have a better concept of what the focus currently is but we are where we are. That is it.

DR. LASKEY: Dr. Zuckerman? No?

DR. ZUCKERMAN: No other comments.

Final Comments from the Sponsor

DR. LASKEY: Dr. Matsumura and colleagues, please.

DR. MATSUMURA: Thank you. I won't take much time because the public speakers have basically taken all the points I wanted to make but there are just two I think I have left. Can you show slide 76?

[Slide]

There was some concern that there may be some missing data at 12 months. I showed accountability of patient visits but we do have accountability for CT and I want to point out that the sites did get CT scans on 199 or 93 percent of patients at 12 months, and that the core lab received 196 of those scans. As pointed out, 40 of those were not evaluable for endoleak; they were evaluated for other things.

As the point has been made, FDA has said that the statistical efficacy endpoint was not made as defined a priori and we have gone over that several times, but I think it is important to realize that there is evolving knowledge in clinical practice. What we thought five years ago was important to look at, we are learning new

things about.

I want to emphasize the clinical data that we presented, the aneurysm-related survival is similar in both groups, which is now the primary outcome measurement as defined by the joint societies.

The clinical effectiveness--there are very few reinterventions, six to seven percent a year, rare conversions and no aneurysm ruptures. I would ask the panel to consider what we consider in 2002 to be measures of effectiveness when they evaluate the efficacy. Thank you.

DR. LASKEY: Thank you, Dr. Matsumura. Dr. Harvey, would you read us the voting options, please?

Recommendations and Vote

DR. HARVEY: Thank you, Dr. Laskey. I will read to the panel their recommendation options for premarket approval applications. The Medical Device Amendments to the Federal Food, Drug and Cosmetic Act, known as the Act, as amended by the Safe Medical Devices Act of 1990, allows the Food and Drug Administration to obtain a recommend from an expert advisory panel on designated medical device premarket approval applications, or PMAs,

that are filed with the agency.

The PMA must stand on its own merits and your recommendation must be supported by safety and effectiveness data in the application or by applicable, publicly available information.

Safety is defined in the act as reasonable assurance, based on valid scientific evidence, that the probable benefits to health under conditions of intended use outweigh any probable risks.

Effectiveness is defined as reasonable assurance that in a significant portion of the population the use of the device for its intended use and conditions of use, when labeled, will provide clinically significant results.

Your recommendation options for the vote are as follows. Number one, approval if there are no conditions attached.

Number two, approvable with conditions. The panel may recommend that the PMA be found approvable subject to specified conditions, such as physician or patient educations, labeling changes, or a further analysis of existing data. Prior to voting, all of the conditions should be discussed by the panel.

Number three, not approvable. The panel

may recommend that the PMA is not approvable if the data do not provide a reasonable assurance that the device is safe, or if a reasonable assurance has not been given that the device is effective under the conditions of use prescribed, recommended or suggested in the proposed labeling.

Following the voting, the Chair will ask each panel member to present a brief statement outlining the reasons for their vote.

DR. LASKEY: Thank you. I now ask for a motion from one of our reviewers. Dr. Comerota?

DR. COMEROTA: Dr. Laskey, I move that the Excluder device be approved with two conditions.

DR. LASKEY: And they are?

DR. COMEROTA: Five-year follow-up on all patients so treated is condition number one. As condition number two, mandatory annual imaging evaluation appropriate to identify aortic aneurysm enlargement, endoleak or wire-form fracture.

DR. LASKEY: As a point of clarification, for the follow-up you want just actuarial survival follow-up, or what other information is included in the follow-up that you are recommending?

DR. COMEROTA: I suppose that is included in the second condition of annual imaging.

DR. LASKEY: Do you want to capture reops or interventions? What should be captured in the five-year follow-up?

DR. COMEROTA: All adverse events.

DR. LASKEY: Okay. We have a motion. We need some discussion and we need to separate the discussion along the lines of the two conditions. Do I have a second for the motion?

DR. PERLER: I second the motion for discussion.

DR. LASKEY: Before we move from there, we do need to separate them out in terms of the two conditions on that motion. So, is there any discussion on the need for the five-year follow-up with adverse clinical events? I think we are all in agreement that that is requisite. If we have agreement, can we have a panel vote on Dr. Comerota's motion to approve with condition one being five-year clinical follow-up? All in favor?

DR. COMEROTA: We are voting on the condition, right? Not on the motion to approve?

DR. LASKEY: That is correct, just on the condition.

DR. PINA: Warren, as an order question, if we want to amend Dr. Comerota's recommendation

and add other conditions is this the time to do it, or do we wait to vote on one and two?

DR. LASKEY: I think we need to do each condition in its own right. So, we will just vote on the present condition and then if we need to add more, we will vote on them. So, can we have a show of hands for the approval for the first condition to the motion for approval, the first condition being five-year clinical follow-up?

DR. BAILEY: Is that for both groups?

DR. LASKEY: For the data set.

DR. COMEROTA: This is approval for patients who will be treated henceforth.

DR. BAILEY: This has nothing to do with the extended follow-up of the current cohort.

DR. LASKEY: They have already stated that they plan to do surveillance on the pivotal clinical data set. This applies to patients in whom this will be implanted from here on. Is that correct?

DR. COMEROTA: Right.

DR. ROBERTS: Wait a minute, we are asking them to follow all patients that get this device for five years?

DR. COMEROTA: That is correct.

DR. LASKEY: For clinical adverse events.

DR. ROBERTS: Oh, I don't think that is possible. I mean, you are saying that every single patient that this device gets put into from hereon that they are going to study those patients?

DR. COMEROTA: I think that what we have recognized, as a medical profession, is that as time goes on after aortic endografts have been implanted there is an increasing number of patients developing complications. I think it is our responsibility to identify those patients, protect them from those complications and to quantify it for any future devices coming on the market. Hence, the reason for the condition.

DR. ROBERTS: Well, I can't vote for that. I mean, that could be hundreds of patients that you are asking the sponsor to spend, you know, hundreds and thousands or millions of dollars trying to follow. I mean, it is very appropriate I think to follow the patients that have already been enrolled in the study, and I would even suggest the ones that were additionally enrolled in the study. But to follow every patient that gets this device, I just don't think that is practical.

DR. AZIZ: Isn't that done for heart

valves and pacemakers?

DR. COMEROTA: It is not unique. We are not precedent setting. It is following precedents for other implantable devices.

DR. ZUCKERMAN: Let me give a point of clarification. To follow every patient who gets a chronic implant for five years post FDA approval would be quite precedent setting. Again, the way that FDA looks at a conditions of approval study or a postmarket study really is what is the scientific question that we are trying to answer, and then to try to develop a sample size and a hypothesis to answer that question, as opposed to, you know, just looking at the whole universe.

6:00 p.m. DR. LASKEY: Well, we can agree we need survival status over the five-year interval. Is that correct?

DR. COMEROTA: Let me try to clarify this. My intent is that we, as clinicians who implant any device or take care of any patients, need to follow our patients properly. I don't necessarily mean to shift that onus onto someone else, other than our own shoulders. Perhaps the message that ought to be conveyed is that once this device, or any endograft, is implanted these patients need careful

follow-up over prolonged periods of time with appropriate imaging studies. Perhaps I didn't word the conditions properly.

DR. PERLER: I misunderstood the condition. I thought you were referring to the pivotal study population. I think one of the problems with accommodating your condition is that often the physician placing the device is not going to be the physician following the patient long term. I think this is not only a logistical and economic challenge for the sponsor but it also is going to be for the physician who places the devices. I agree with Anne, I don't think it is doable.

DR. COMEROTA: Who is going to take that responsibility? Would you argue that it needs to be done, Bruce?

DR. PERLER: Oh, I agree and I try to do it with my patients and communicate what I think needs to be done when those patients are not being followed by me. I think we certainly can urge the company to inform those practitioners placing devices that they need to follow the patients or if they are not, to communicate what needs to be done to the patient's primary physician.

DR. COMEROTA: Well, I will tell you that the institution where I currently reside--I am impressed that your initial observation is true that primary referring physicians fall down significantly. I will also tell you that there is a responsibility that is assumed by the physicians who put the device in to make sure that those follow-up visits are properly performed. And, I will also tell you that there are graft-related problems that have been identified in asymptomatic patients over long-term follow-up because of this dogged pursuit of good follow-up. So, whose responsibility is that? I am not necessarily trying to shift the responsibility from the physician, but I am saying that it needs to be done, especially in devices such as this that have been demonstrated to increase problems over time.

Somehow, I think, we need to integrate that into a recommend. Now, it may not have to be the responsibility of the manufacturer, but it has to be one of the patient care provider's responsibilities.

DR. ZUCKERMAN: Let me interject here. Usually the way that those points are brought into a recommendation is through adequate labeling, both

in the IFU and the patient labeling, and also perhaps an appropriate design of a postmarket study that can answer specific scientific questions. But there is a line where the notion of professional responsibility for physicians still has to be accepted. The agency has to be cognizant that it can't replace the role of physicians.

DR. LASKEY: It is interesting that at the outset of this meeting the very first thing we heard about was a large-scale registry in which every patient with device implanted would be followed voluntarily, and so forth. So, there is certainly a movement within the profession to obtain long-term detailed follow-up with hundreds of data fields in these databases. So, I don't think this is very far off the mark, but we are aware of the onus put upon the third party.

DR. SIDAWY: Yes, and I don't think we should forget that since there are no such conditions placed on other manufacturers of similar devices, I think placing such a condition on the sponsor will have a differential advantage or disadvantage in marketing these devices. We should strongly suggest to the people who are implanting these devices, physicians, to recommend to them to

voluntarily report to such registries and ask them to follow these patients, but I don't think we should place that condition on the sponsor.

DR. LASKEY: As a consequence of this discussion, are we moving towards a distillation of your first condition to involve survival over five years, or where are we going with this?

DR. COMEROTA: Let me try to clarify that, Warren. Perhaps it would be best included in a labeling recommendation rather than a condition for approval. I think that wording and that guidance is very appropriate, and I would be very happy to either modify it or withdraw the condition.

DR. LASKEY: You need not withdraw it; you can just apply it to labeling. That would be a different condition, to have that language applied to labeling.

DR. COMEROTA: I would so modify that to have the five-year follow-up, a minimum of a five-year follow-up applied to a labeling condition as a recommendation to physicians.

DR. LASKEY: Discussion on that?

DR. PINA: This is supposing that the sponsor will continue following the patients in the pivotal trial?

DR. COMEROTA: Right.

DR. PINA: I mean, I would like to see the five-year data on the pivotal trial, both the control group and the study group.

DR. ROBERTS: I think that is what the condition should be. I mean, they have said that they will do that but it probably should come from the panel as a condition that they have to do that; that there has to be a follow-up of the study patients over five years, with a report on a yearly basis regarding the appropriate parameters and, presumably, that is aneurysm rupture, adverse events, endoleaks, increased size of the aneurysm, those types of things. I think that it probably ought to go into there.

I am a little concerned, quite frankly, about this idea of somehow putting in the labeling that patients have to be followed for five years with data collected, or something. I am not sure actually that is appropriate for the labeling. It may be something that is more appropriate in the training, when the company goes to set up their training materials that something should be in there that is, you know, encouraged or strongly suggested that the information from the patients be

entered into the registry, or something along those lines.

DR. PINA: Actually in the patient brochure as well because I think the patients need to be educated that follow-up is critical, and the suggestion that follow-up be done by the physician.

DR. LASKEY: That came up with Julie's point in the patient information package. We have moved now to approvable with one condition, which is that there be comprehensive mandatory five-year follow-up in the pivotal clinical data set, to include not just survival status but specific radiographic information. Do you want to further specify what that is, and are we going to write in here CT, MRI? Where will we stop?

DR. FREISCHLAG: I would recommend for this pivotal group that we put those in because, obviously, we spent a lot of time asking where those were today, and I think this would be great and make a lot of us, especially me, feel good. If we did specify we want CT scans and KUBs in these patients really for five years, it certainly would make me feel good, and I think we also would get a great data set.

DR. BAILEY: Perhaps we could add with

appropriate attention to missing data and description thereof.

DR. LASKEY: Okay, we have approvable with a single condition, comprehensive in its scope but requiring five-year follow-up clinical and actuarial. Is that a reasonable approach?

DR. COMEROTA: For condition number one.

DR. LASKEY: Well, we are folding number two in. We are folding the radiologic information into the follow-up information.

DR. COMEROTA: Actually no, my intent for condition number two was that the treating physician or the person responsible for patient care provide an appropriate imaging modality to identify aortic aneurysm enlargement, endoleak or wire fracture at least for five years on an annual basis. That would be included in the recommendations for use.

DR. NAJARIAN: I think it is somewhat too structured to recommend a time frame. I think that is something that could be put in the labeling or even the training, that it is highly recommended that patients be followed with KUB and CT on a one-month, six-month and then yearly basis, and leave it at that.

DR. COMEROTA: Okay, that is acceptable.

DR. LASKEY: Then let's vote on the first condition. Do we have consensus on the first condition at least, which was the comprehensive five-year follow-up for the pivotal data set? Let's see a show of hands.

[Show of hands]

All right, unanimous approval for the first condition. Now, for your second condition, I am a little unclear on the nature of this.

DR. COMEROTA: In terms of part of the labeling, the recommendations for use, Ken, did you want to rephrase the condition?

DR. NAJARIAN: There are several things we want to put into the labeling. I don't know that those need to be conditions. Maybe we could discuss those. Everybody brought up some pretty good points on the labeling. One thing on the labeling I think Tony is trying to get at is that it is highly recommended that the patients have adequate imaging follow-up, or suggested at, you know, one-month, six-month and yearly intervals, and that follow-up should include CT and KUB. Of course, that is at the discretion of the implanting physician and patients will be lost to follow-up.

DR. COMEROTA: That worries me. I am not so sure it should be at the discretion of the implanting physician. You can't just put a graft in like this and say good-bye. We will see you whenever we see you.

DR. NAJARIAN: But there is a responsibility that we all have as physicians, and I don't think you want to dictate clinical practice or how people follow their patients.

DR. COMEROTA: But you always dictate clinical practice by the indications for use.

DR. LASKEY: I am not sure the FDA or we can mandate any of this.

DR. COMEROTA: Well, we are recommending.

DR. NAJARIAN: I understand what you are trying to get at but, again, the purpose of this committee is to decide on the safety and effectiveness, and that data is here before us now and we have recommended a five-year follow-up of the patients in the pivotal study and that should get us somewhere.

DR. ROBERTS: If you look at the labeling, number three, under completion of the procedure, it says follow up patients as necessary to provide proper surveillance of long-term procedure of the

endoprosthesis procedure and status of the aneurysm. Annual CTs and various views of x-rays may be used for such surveillance. I think that that sort of almost gets it, but I think it has to be stronger and that instead of follow up patients, it should be something like patients must undergo surveillance of the long-term performance of the endoprosthesis. The FDA will probably work that language, but I think that what we need to recommend is that it really be forcefully indicated in the label that these patients need to undergo follow-up on an annual basis.

DR. COMEROTA: And, I am not suggesting the imaging modality. If, four years out, the patient has a cardiac cath and there is an IVUS being passed and you can look at the graft with the IVUS in the process of doing the cardiac cath, that is great; that is good imaging modality and it may be appropriate. We don't know what ultrasound will be. We don't know what MRA or MRI will be in the future and they may be appropriate. So, we are not dictating the imaging modality. I am only suggesting that these patients need to be objectively followed on a routine basis for the long term.

DR. WHITE: I am really afraid we are overstepping our bounds. I think I would not like to have my practice regulated by an indication for use. I would not like to have a plaintiff attorney running around saying, Dr. White, why didn't you follow this? Why am I responsible for the guy who leaves my territory or goes some place else?

I am not arguing with what you are saying, Tony, as being good clinical practice but I think that putting it down in an indication for use is probably not the right way to get physicians to do it.

DR. ROBERTS: It is already in there, Chris.

DR. WHITE: Required to be followed?

DR. ROBERTS: Well, read number three, indications for use, it basically says that. We are just saying it needs to be a little stronger.

DR. LASKEY: We may not then need to make this a condition. I don't know what you think, Dr. Zuckerman, but it doesn't sound like there is enough oomph here to make this a condition. If it is a fine-tuning of the language, I guess that is something we can live with.

DR. ZUCKERMAN: Yes, you know, one

possibility is that a condition of approval would be that the FDA would seriously look and the sponsor would seriously look at all the labeling comments suggested both during this present discussion and the prior discussions regarding fine-tuning of the indications etc.

DR. SIDAWY: Mr. Chairman, I would like to recommend that the FDA look at the language that they have for other manufacturers and use the same language for this one.

DR. LASKEY: Again, that need not be a condition. I think you can do that off line. I think we simply have one condition on this motion, which at the present time makes life easy.

DR. FREISCHLAG: I would like to make a suggestion which is a little bizarre. Could a condition be that those 40 CT scans that we know exist, that we know were mailed, can they be reviewed and that data reported to us so that we get the 196? I think she gave me a window when she said that it is not normal to do that but they have the 40 scans; they just didn't like the way they looked. Can't they reprocess? They are all on computers. They can be re-looked at. I have a feeling they all could do that tomorrow if we asked

them, and that would make me feel great. So, I would like to make a condition that the 40 CT scans that we know were mailed to Cleveland be reviewed and that data given to us on endoleaks.

DR. LASKEY: Or given to the FDA. That is not unreasonable to complete the data set.

DR. ZUCKERMAN: No, frequently that is requested by the panel if the data are available.

DR. LASKEY: Can we vote on the second condition? Actually, the motion was made for a condition, can I hear a second?

[The motion was duly seconded]

All in favor of the second condition, that being the acquisition of the outstanding serial CT data? All in favor?

[Show of hands]

Unanimous. Thank you. That is two conditions.

DR. PINA: This is the time to enter a third condition. I would like to move that the physician education packet be amended to stress the source of the mortality and the co-morbidities, and to stress to the practicing practitioner who is inserting the graft that these patients need to continue to be followed very closely either by a

cardiologist or by their primary care physician, but with close attention paid to the co-morbidities, and that these items of close follow up be added to the patient education booklet as well.

DR. LASKEY: It sounds reasonable. Certainly, the latter is easy to do, to fold that into the patient brochure and make it clear about the follow-up with their doctor. I don't know about the first one though, how we can craft that language to basically be a diligent physician.

DR. PINA: Well, you may want to leave it to the FDA to craft the language but I think the point needs to be made that the morbidity and mortality is not always directly related to the graft itself but perhaps to the co-morbid conditions and that they cannot be overlooked. So, they can certainly put that in the physician instruction. That is not mandating practice; it is recommendation, not mandating.

DR. LASKEY: Do we need to vote on this one? It is kind of soft. Do you want to make it formal?

DR. PINA: Yes, I want to make it formal.

DR. LASKEY: May I hear a second to Dr.

Pina's motion to institute language along the lines of scrupulous attention to cardiovascular risk factors following implantation?

[The motion was duly seconded]

Thank you. All in favor?

[Show of hands]

Dr. Pentecost, no?

DR. PENTECOST: No.

DR. LASKEY: Thank you. That is condition three.

DR. AZIZ: Warren, let me just ask a question. Once those 40 scans are reviewed and you find some disconcerting data, what happens?

DR. FREISCHLAG: The plan is that is not going to happen.

DR. AZIZ: Seriously, what do you do then?

DR. FREISCHLAG: They would probably have to let us know about it.

DR. ZUCKERMAN: The usual tack that the agency takes is that there would be an internal review. If the data are appropriate and consistent with what has been discussed today, the agency would probably handle the situation internally. But if there are big problems that develop we always have the option of going back to panel and

discussing these data.

Dr. Laskey, on the last motion I wasn't sure of the vote, motion number three by Dr. Pina.

DR. LASKEY: Condition number three, you mean the language or the vote?

DR. ZUCKERMAN: I am not sure that the vote is a positive one. I didn't see all hands up.

DR. LASKEY: We need to raise our hands higher, folks.

[Show of hands]

That condition carries.

DR. ZUCKERMAN: Thank you.

DR. LASKEY: Additional conditions? We have had it! I would now ask Dr. Harvey to restate the conditions of approval in order to have the panel make a final vote.

DR. HARVEY: All right, I will paraphrase here. The first one was mandatory five-year follow-up on all the patients in the pivotal study cohort.

DR. LASKEY: Recommend approval with the following conditions.

DR. HARVEY: Right.

DR. LASKEY: Number one?

DR. HARVEY: The first condition was

mandatory five-year follow-up on all the patients in the pivotal study cohort. The second condition was to obtain the outstanding information on the 40 CTs. That information should be submitted to FDA, reviewed and reported to the panel. The third condition was that the IFU should stress the sources of co-morbidities and mortality, and that the patient labeling or brochure should include this information as well.

DR. ZUCKERMAN: Let me ask one question. On condition number two, is it that the 40 CT data should be obtained and reviewed, not necessarily brought back to panel unless major questions arise.

DR. LASKEY: Right.

DR. HARVEY: So to clarify it, it should be brought back to the agency and reviewed by the agency.

DR. NAJARIAN: I just have a question. As far as conditions, did we address in the condition the external iliac artery size, and should that be a condition? That is in the label?

DR. ROBERTS: Yes. I wouldn't make that a condition but definitely I think the FDA has heard the concern about the iliac--

DR. LASKEY: Recommendation that the

dimensional data be put in.

DR. ROBERTS: Yes, and I would, just so it doesn't get lost, also recommend--and I am not going to make this a condition for approval, but also recommend that the patient brochure really indicate to the patients the fact that there may be follow-up that needs to be done in terms of imaging follow-up but then also perhaps in terms of therapy so that they don't have a false idea of what they are getting into.

DR. HARVEY: So, based on those three conditions and the motion for approvable with those conditions, we can now take a vote.

DR. LASKEY: We will do a show of hands and then we will go around and we will adjourn. Can we have a show of hands to support the recommendation to approve with those three conditions?

[Show of hands]

DR. HARVEY: If we could go around the table and hear the person's vote and their reason for that vote.

DR. AZIZ: I think the device has been shown to be safe, but I do have some concerns about the 40 patients that were missing but I think now

that the data will be provided and looked at, and could influence what the FDA recommends I feel satisfied to approve it with conditions.

DR. COMEROTA: The reason for my vote was based upon 19 centers, 19 investigators implanting the device with 100 percent success rate, no aneurysm rupture in follow-up, no conversions in the first two years, and only three conversions thereafter, translating to less than 1.5 percent conversion rate in more than two years; significantly fewer adverse events than operated patients in this prospective trial. While bothered by less than 100 percent follow-up of CT scans, realizing that many prospective randomized trials, when imaging modalities are used as an endpoint, oftentimes there is somewhere between a 20-40 percent drop-off rate in evaluable imaging modalities over time. So, this seems to fit with what we have seen in the literature, and I think the bottom line is this device is good for patients.

DR. PENTECOST: I would support this and echo the sentiment very confidently that I think this is a good device for patients. I think we have heard a lot about endoleaks and also the

dynamics of aneurysms after they have been stented over the last five years. So, I think we can be excused for not having thought of all these criteria up front, but we don't have any excuse for it now and I think we need to be very scrupulous in the way we follow patients with endoleaks over time. The agency should insist on that, and we should also look very carefully at the dynamics, the measurements etc. of the aneurysmal sac which persist after these are in place.

DR. BAILEY: I voted for approval. I believe this device does represent a useful option for patients based on the data that have been presented; that there are fewer acute problems than with surgery. I think the efficacy issue and what the number is, is not a trivial issue but I think despite the presentation which I think could have been a lot clearer, there is significant evidence of reasonable efficacy. I don't think it is fair to say it is 80 percent but I think it is reasonably high. So, almost sort of despite the confusing presentation, I think there is a good product there. I would just encourage a more clear presentation of the efficacy data which I do think is important.

DR. SIDAWY: I voted affirmatively because I felt that this device will give a good option to the patient. It has some characteristics in ease of deployment that may differentiate it from other devices available. My concerns were related to the absence of the CT scans and the condition that we voted on satisfies that and, therefore, I voted affirmatively on this device.

DR. FREISCHLAG: Ditto. I voted yes for similar reasons as Tony, and have confidence that the follow-up will be excellent by the Gore company for us to learn more about how aneurysms change over time. I think that is what we have learned from the last two years when these devices have been approved. There is a lot more that goes on after the device is put in and before the device is put in, and we just need to pay attention.

DR. NAJARIAN: Yes, I voted for approval with the conditions. I think the sponsor has done a very good job of showing us that this is a safe and effective device even though we have had some difficulty with the statistics. I am not sure I remember which one is the numerator or the denominator anymore; I have to review that when I get home. But I think it is probably going to be a

very good device and very applicable in this patient population.

DR. ROBERTS: I voted for approval because I am also impressed with the ability of the operators to get the device in place in all of the patients, as well as the safety profile of the device compared to the control, and I think that, hopefully, with good follow-up we won't be disappointed with our vote.

DR. PERLER: Well, I voted for approval. Based upon my clinical experience and based upon the data presented today, I am convinced this is a safe and effective device. The fundamental question for me is very simple, would patient care be advanced by approval of this device or rejection, and I think that is a very easy question. I think it is going to be advanced and that is why I voted that way.

DR. WHITE: Too late to change?

[Laughter]

I find myself in the position of minority. I know that this is a good device and I know that it has been implanted with tremendous success. In fact, I am always suspicious about 100 percent success. Be that as it may, I don't think it met

the criteria for the approval and there had to be a reasonableness of efficacy, and I believe that just on the face of the data the reasonableness of efficacy was not shown and so I voted no.

DR. PINA: I think that keeping older patients away from surgery that very often brings other complications is a good thing. So, I think that overall this is going to add to the patient care in this population that tends to be more frail, and the ability to get them up and moving earlier and getting them back to their regular activities is a benefit. I have been concerned, as Dr. White has been, with the missing CT scans and, hopefully, with our conditions these will be met and, hopefully, better physician and patient education as well.

DR. LASKEY: Thank you, colleagues. Any final words from Mr. Dacey and Mr. Balo?

MR. DACEY: No.

MR. BALO: I really think, from my perspective, you know, we spent a lot of time going through a lot of details and trying to get a better clarification of the data, but I do agree with what was said today, that the sponsor has done an outstanding job not only following up for 12 months

but actually going out to 24 months, and taking into consideration some of the concerns which have just been brought up about the grafts and things that occur after they are implanted. So, I think also that what Dr. Pina said relative to people being ambulatory, spending time in the ICU and just better healthcare for the patient overall, I believe this device will be able to provide that for patients.

DR. LASKEY: Thank you. Our appreciation again to Gore and their representatives, thank you very much, gentlemen, and to the FDA support staff.

DR. HARVEY: I would just like to make a point of clarification. The talk that was scheduled by FDA's Office of Surveillance and Biometrics at 4:30 has been moved to tomorrow's agenda.

DR. LASKEY: We are adjourned.

[Whereupon, at 6:25 p.m., the proceedings were recessed, to resume at 8:00 a.m., Tuesday, September 10, 2002.]

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CERTIFICATE

I, **ALICE TOIGO,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

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